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Prevalence of Asymptomatic Carotid Artery Stenosis According to Age and Sex

Systematic Review and Metaregression Analysis

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Background and Purpose—In the discussion on the value of population-wide screening for asymptomatic carotid artery stenosis (ACAS), reliable prevalence estimates are crucial. We set out to provide reliable age- and sex-specific prevalence estimates of ACAS through a systematic literature review and meta-regression analysis.

Methods—We searched PubMed and EmBase until December 2007 for studies that reported the prevalence of ACAS in a population free of symptomatic carotid artery disease. Data were extracted with use of a standardized form on participants' characteristics, assessment method, study quality, and prevalence estimates for moderate (≥50% stenosis) and severe (≥70% stenosis) ACAS. Metaregression was used to investigate sources of heterogeneity.

Results—Forty studies fulfilled the inclusion criteria. There was considerable variation among studies with respect to demographics, methods of grading stenosis, and stenosis cutoff point used. The pooled prevalence of moderate stenosis was 4.2% (95% CI, 3.1% to 5.7%). Prevalence of moderate stenosis among people age <70 years was 4.8% (95% CI, 3.1% to 7.3%) in men and 2.2% (95% CI, 0.9% to 4.9%) in women. Among those ≥70 years, prevalence increased to 12.5% (95% CI, 7.4% to 20.3%) in men and 6.9% (95% CI, 4.0% to 11.5%) in women. Metaregression showed that both age and sex significantly affected the prevalence of moderate stenosis. No contribution of study size, publication year, geographic region, assessment method, and study quality was found. The pooled prevalence of severe stenosis was 1.7% (95% CI, 0.7% to 3.9%).

Conclusions—Prevalence of moderate stenosis increases with age in both men and women, but men at all ages have the higher prevalence estimates. The number of studies that allowed meaningful data synthesis of severe stenosis was limited. **(*Stroke*. 2009;40:1105-1113.)**

Key Words: asymptomatic carotid artery stenosis ■ prevalence ■ systematic review ■ metaregression analysis

Stroke is the leading cause of death and hospitalization in both men and women in nearly all European countries and the third major cause of death in the United States.[1,2] Carotid artery stenosis is 1 of the risk factors for stroke.[3,4] Studies have reported an annual risk of stroke of ≈2% to 5% for patients with severe asymptomatic carotid stenosis.[4–7]

Carotid endarterectomy is 1 of the most common vascular surgery procedures, and it reduces the risk of stroke in patients with symptomatic carotid stenosis.[8,9] However, despite the publication of several randomized, controlled trials in asymptomatic patients,[10,11] the role of carotid endarterectomy and noninvasive screening is still debated,[12–14] in part because accurate estimates of the prevalence of carotid stenosis in different risk groups are missing. This precludes planning of effective screening and treatment of populations at (high) risk of severe asymptomatic carotid stenosis who might benefit from preventive surgery. We set out to provide reliable age- and sex-specific prevalence estimates of asymptomatic carotid artery stenosis through a systematic literature review and a meta-analysis.

Methods

Search Strategy

We performed a PubMed and EmBase search to retrieve all published articles reporting on the prevalence of asymptomatic carotid artery stenosis from 1966 until December 2007. The following keywords were used: carotid arter* diseas* (title/abstract), carotid arter* stenos* (title/abstract), carotid stenos* (title/abstract), or carotid arter* atheroscleros* (title/abstract) combined with prevalence (all fields), frequency (title/abstract), or occurrence (title/abstract). A cross-reference check was performed to ascertain additional articles.

Study Eligibility

We reviewed the abstracts to identify studies that satisfied the following predefined inclusion criteria. First, studies must have

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Table 1. Overview of Selected Articles

First Author	Year	Population	No. of Individuals	Age Range, y	Mean Age, y	Female, %
Chan[16]	1983	One friend control was selected by each diabetic; Seattle, Wash	135	35–74	60	53
van Merode[17]	1985	Population sample Maastricht area, The Netherlands	93	50–69	ND*	0
Josse[18]	1987	Patients referred for ultrasonic examination of cervical arteries, Paris area, France	526	45–84	ND	58
Ramsey[19]	1987	Volunteers from church congregation, Illinois	102	50+	ND	56
Colgan[20]	1988	Volunteers at health fairs, Illinois	348	24–91	61	60
Langsfeld[21]	1988	Volunteers at health fairs, Australia	153	40+	56	48
Salonen[22]	1988	Population sample Kuopio area, Finland	412	42–60	51	0
Jungquist[23]	1991	Birth cohort of Malmö, Sweden	478	69	69	0
Bots[24]	1992	Subsample of the Rotterdam study, The Netherlands	954	55+	ND	ND
O'Leary[25]	1992	Population sample Framingham, US	1189	66–93	ND	ND
O'Leary[26]	1992	Subcohort of Cardiovascular Health Study, US	5116	65+	ND	57
Prati[27]	1992	Population sample Friuli-Venezia Giulia region, Italy	1348	18–99	ND	53
Puija[28]	1992	Elderly from retirement homes, Seattle, Wash	239	65–94	ND	76
Sutton-Tyrrell[29]	1993	Normotensive control subjects of SHEP, Pittsburgh, Pa	187	60+	ND	59
Willeit[30]	1993	Population sample Bruneck, Italy	909	40–79	ND	49
Fabris[31]	1994	Population sample, Turin, Italy	457	18–97	55	49
Lindgren[32]	1994	Control subjects, Lund, Sweden	59	51–95	72	49
Pascazio[33]	1994	Normotensive controls matched for age, sex, and cardiovascular risk factors, Trieste, Italy	71	64–91	73	35
Aronow[34]	1995	Elderly in a long-term health care facility, US	1275	60–101	81	71
Auperin[35]	1996	Population sample Nantes, France	1279	59–71	65	59
Harer[36]	1996	Population sample Moscow, Russia	529	36–84	58	35
Beks[37]	1997	Normal glucose tolerance group of the Hoorn Study, The Netherlands	287	50–74	63	48
Mannami[38]	1997	Population sample of Suita, Japan	1445	50–79	63	53
Martyn[39]	1998	Birth cohort of Sheffield, UK	181	±70	68	33
Rodriguez-Saldana[40]	1998	Population sample of CUPA project, Mexico City, Mexico	198	60+	ND	72
Cheng[41]	1999	Healthy controls, Hong Kong, China	108	50+	62	61
Meissner[42]	1999	Population sample Olmsted County, Minn	567	45+	ND	ND
Hillen[43]	2000	Healthy volunteers Berlin Ageing Study, Germany	225	70–100	80	41

(*Continued*)

Table 1. Continued

Exclusion Criteria	Stenosis Criteria	Assessment Method†	Classification of Stenosis‡	No. of Quality Criteria§	Prevalence of Moderate Stenosis (≥50%)	Prevalence of Severe Stenosis (≥70%)
–	<50%, ≥50%	2	2	0	0.7	–
IDDM, unavailable lipid profiles	≤15%, 16–49%, 50–99%, 100%	1	2	3	5.4	–
Coronary and/or peripheral vascular diseases, risk factors for atherosclerosis	<15%, 15–50%, ≥50%	2	2	0	2.1	–
–	<20%, 20–39%, 40–59%, 60–79%, 80–99%, 100%	2	2	0	–	1.0
Cerebrovascular/ocular symptoms	1–15%, 15–49%, 50–79%, ≥80%	2	2	0	3.7	0.9
–	0–20%, 21–49%, ≥50%, 100%	2	2	0	1.3	0.7
–	≤20%, >20%	2	1	1 (3)	–	–
–	0–29%, 30–59%, ≥60%	1	2	2 (2, 3)	–	3.1
–	0%, 1–15%, 16–49%, ≥50%	2	2	3	1.4	–
ND	0%, 1–24%, 25–49%, 50–74%, 75–100%	2	2	2 (1, 2)	7.6	2.4
–	0%, 1–24%, 25–49%, 50–74%, 75–99%, 100%	2	2	3	6.2	1.6
Stroke survivors	<40%, ≥40%	2	2	3	–	–
–	1–49%, 50–99%, 100%	2	2	1 (3)	4.6	–
Recent MI, stroke, heart failure, PAD, TIA, contraindication to study medication, systolic blood pressure <160 mm Hg	<50%, ≥50%	2	2	0	7.0	–
CEA, TIA/CVA, missing lab data	<40%, 40–80%, ≥80%	2	1, 2	3	–	1.8
–	<25%, 25–49%, 50–75%, 76–99%, 100%	2	1	3	3.9	0.9
Stroke, TIA	<50%, 50–99%, 100%, 80–99%	2	2	2 (1, 2)	13.6	0
Not free from coronary or cerebrovascular disease	<20%, 20–49%, ≥50%	2	2	0	7.0	–
–	<40%, 40–80%, 81–99%, 100%	2	2	0	–	3.5
CVA	0–20%, 20–40%, >60%	2	1	2 (1, 2)	–	–
ND	<50, 50–60%, 70–80%, 90–95%, 100%	1	2	0	4.2	2.8
Diabetes mellitus, impaired glucose tolerance	0–15%, 16–49%, ≥50%	2	2	2 (2, 3)	2.8	–
–	<25%, 25–50%, >50%	2	1, 2	1(2)	4.4	–
–	0%, 1–30%, 31–50%, >50%	2	1	0	8.8	–
ND	≤50%, >50%	2	?	?	6.1	–
–	0–29%, 30–69%, 70–99%, 100%	2	2	0	–	0
–	≤49%, 50–79%, 80–99%	2	2	2 (1, 2)	8.1	0.4
Immobility, need of help or incontinence	≤50%, 51–75%, >75%	2	2	2 (2, 3)	15.1	4.0

(*Continued*)

Table 1. Continued

First Author	Year	Population	No. of Individuals	Age Range, y	Mean Age, y	Female, %
Mannami[44]	2000	Population sample, Ikawa, Japan	249	50–69	60	0
Mathiesen[45]	2001	Population sample Tromsø Study, Norway	6420	25–84	ND	53
Su[46]	2001	Normotensive adults from the Chin-San Community Cardiovascular cohort, Taiwan	270	35+	64	58
Lernfelt[47]	2002	Birth cohort of Gothenburg, Sweden	142	78	78	50
Mineva[48]	2002	Population sample of the city of Stara Zogara, Bulgaria	500	50–79	ND	60
Luedemann[49]	2002	Population sample of northeast region of Germany	1632	45–70	58	53
Wang[50]	2002	Offspring and spouses of offspring of Framingham Heart cohort, US	3173	25–90	55	52
Rosvall[51]	2002	Subcohort of Malmö Diet and Cancer study, Sweden	4208	46–68	ND	57
Alkaabi[52]	2003	Matched controls of rheumatology outpatient clinics, Dundee, UK	40	36–73	55	50
Horner[53]	2005	Subsample from the Austrian Stroke Prevention Study	500	50–70	ND	ND
Takahashi[54]	2005	Matched controls of the HIMEDIC Imaging Center, Japan	605	54+	63	34
Hupp[55]	2007	Vascular screening program in Annapolis, Md	11 636	40–95	65	59

IDDM indicates insulin-dependent diabetes mellitus; MI, myocardial infarction; PAD, peripheral artery disease; TIA, transient ischemic attack; CEA, carotic endarterectomy; and CVA, cerebrovascular accident. Because the majority of studies did not report the method of measurement (ie, NASCET or ECST method) of stenosis, a column with this information was not added. When the method of measurement was reported, the NASCET method was used.

*Not documented.

†1=Doppler, 2=duplex.

‡1=Lumen diameter reduction, 2=peak systolic velocity method.

§1=Representation of the general population, 2=appropriate recruitment of the population (random or consecutive), 3=adequate response rate (≥50%).

evaluated a population free of symptomatic carotid artery disease. Conversely, studies on patients with clinically manifest vascular disease or those at high risk for vascular events were excluded. Studies with information on the prevalence of asymptomatic carotid stenosis in the control groups of a clinical trial resembling the general population were also included. Second, studies were required to have reported sufficient detail to allow estimating the prevalence of stenosis. Thus, studies with measurements of carotid intima-media thickness of plaques only were not included. We included cross-sectional and cohort study designs and articles in any language. Studies were included only once if there were multiple publications concerning the same study population.

Data Extraction

Two investigators (M.d.W. and A.W.F.d.J.) selected the studies to be included in the review, extracted the data independently, and cross-checked them, with disagreement resolved by discussion with a third reviewer (either J.P.G. or M.L.B.). The following data were extracted from each study: description of the population characteristics (publication year, type of population, country, number of included participants, age range, mean age, sex distribution), assessment method, method of measurement of carotid stenosis, and carotid stenosis prevalence estimates. Data were extracted with the use of standardized data extractions forms specifically created for this review and were subsequently entered into a database. Where mean age was not stated, the population weighted mean or midpoint of the range was derived. Because different cutoff points for stenosis were used, we distinguished the following categories: moderate stenosis (≥50%) and severe stenosis (≥70%).

Quality Assessment

Quality of all selected articles was assessed by 1 of the investigators (J.P.G.) for the following attributes: representation of the general population, appropriate recruitment of the population, and adequate response rate. In prevalence studies, the participants selected ideally should be representative of the general population. Methods of achieving this may involve using population registries, inhabitants of a defined area, and people registered with a general practice. Participants attending health checkups may be biased and only cover certain population groups. Recruitment was considered appropriate if recruitment of participants was random or consecutive rather than performed for convenience. A response rate of 50% or higher was considered adequate.

Data Analysis

Prevalence estimates were, wherever possible, stratified by age and sex for each study. Outcome measures were pooled across studies with use of a random-effects model, which allows for heterogeneity of effects between studies.[15] To test our hypothesis concerning the effect of age and sex, a metaregression model was built with prevalence estimates of moderate stenosis as the dependent variable. The covariates in this model were participants' mean age, percentage

Table 1. Continued

Exclusion Criteria	Stenosis Criteria	Assessment Method†	Classification of Stenosis‡	No. of Quality Criteria§	Prevalence of Moderate Stenosis (≥50%)	Prevalence of Severe Stenosis (≥70%)
–	<25%, 25–49%, ≥50%	2	1, 2	0	9.6	–
Persons from previous dietary trial	<35%, ≥35%	2	2	3	3.4	0.9
–	<50%, ≥50%	2	2	2 (2, 3)	1.5	–
People who lived in nursing homes	≤50%, 51–75%, >75%	2	2	1 (3)	22.5	4.9
Clinical signs and symptoms of vascular diseases	0–49%, 50–79%, 80–99%	2	2	1 (2)	6.4	0.4
Without cerebrovascular symptoms						
History of MI or stroke, complete data	≤50%, >50%	2	2	1 (3)	2.0	–
–	<25%, ≥25%,	2	2	2 (1, 3)	–	–
Technical problems with duplex scan, missing lab data, homemakers	<15%, ≥15%	2	1	2 (1, 2)	–	–
History of inflammatory arthritis or vascular disease	<20%, 20–49%, 50–74%, ≥75%	2	1	0	0	0
Not free from previous cerebrovascular attacks	<50%, 50–70%, >90%	2	?	1 (1)	1.2	0.4
History of neurologic disorder, abnormal neurology manifestation	<25%, 25–49%, ≥50%	2	1	0	2.0	–
–	1–39%, 40–59%, ≥60%	2	2	0	–	–

of women, study size, publication year, geographic region, assessment method (Doppler versus duplex), and several quality indicators. Publication bias was examined visually with a funnel plot of study precision against effect size and statistically by Egger's test. A deficiency in the base of the funnel with asymmetry indicates the presence of possible publication bias from unpublished small studies. Statistical analyses were performed with SAS (version 9.1) and STATA (version 8.0).

Results

Figure 1 shows the consecutive steps that were followed to identify the appropriate studies. We identified 40 studies that fulfilled all inclusion criteria.[16–55] Table 1 summarizes the characteristics of these studies. One of these publications was in Spanish,[40] and the remaining 39 were in English. Three studies[26,45,55] examined >5000 individuals and contributed almost 50% of the total number of individuals. There was a considerable variation among studies with respect to demographics (age and sex distribution), methods of grading stenosis, and the stenosis cutoff point used. Study quality assessment revealed deficiencies in many areas of methodology. Seven studies met all 3 quality criteria, 10 studies met 2 criteria, 7 met 1 criterion, and the remaining 15 studies met no quality criterion (Table 1).

Moderate Carotid Artery Stenosis

From 29 studies, we obtained data on 22 636 individuals, including 959 persons with moderate carotid artery stenosis (≥50%).[16–18,20,21,24–26,28,29,31–33,36–40,42–49,52–54] Prevalence of moderate stenosis ranged from 0% to 22.5%, with a pooled random-effects prevalence estimate of 4.2% (95% CI, 3.1% to 5.7%; Figure 2). Restricting our analysis to only population-based studies[17,24–26,31,32,42,45,53] resulted in a similar pooled prevalence estimate of 4.1% (95% CI, 2.4% to 6.8%).

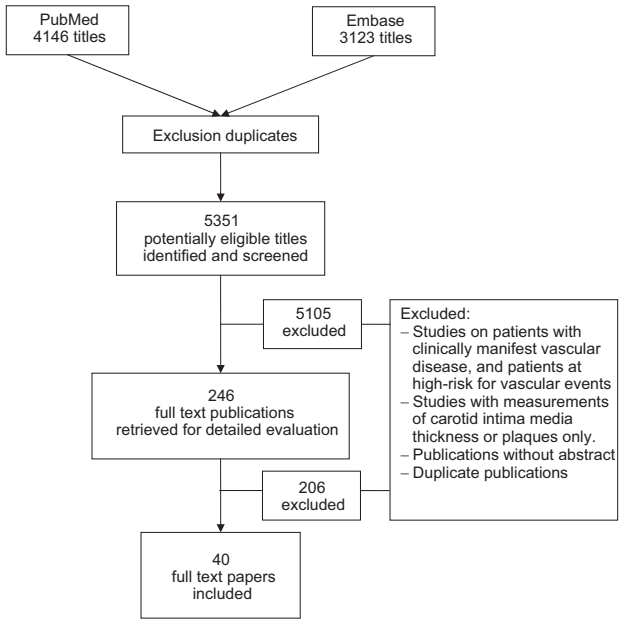

Figure 1. Results of search strategy.

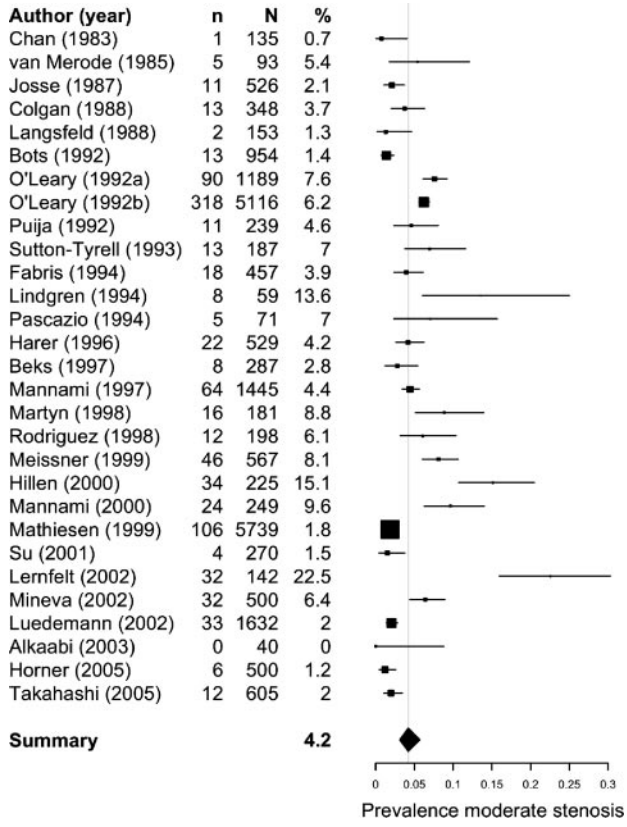

Figure 2. Prevalence of moderate asymptomatic carotid artery stenosis (≥50% stenosis). Bars indicate 95% CI on the proportion.

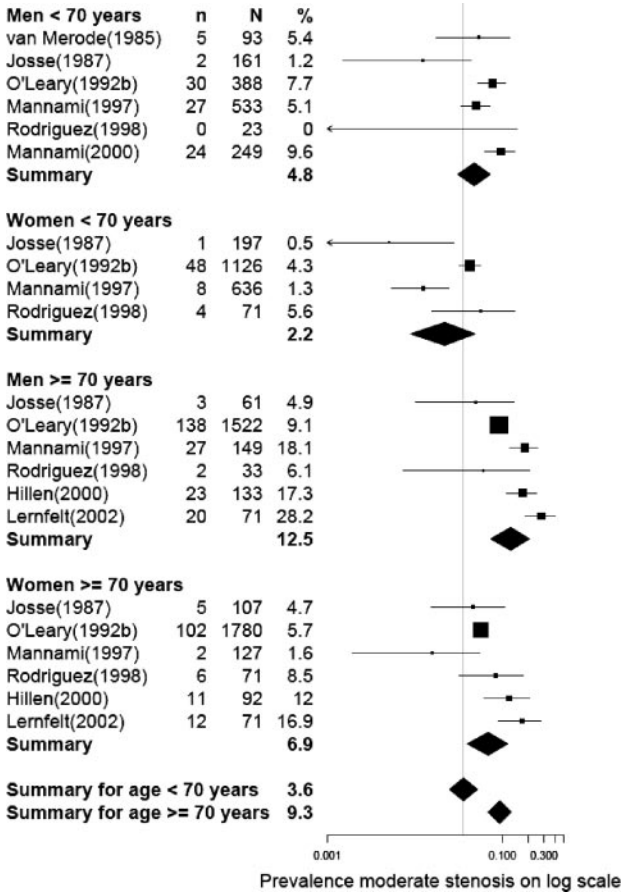

Figure 3. Prevalence of moderate asymptomatic carotid artery stenosis (≥50% stenosis) stratified according to age and sex wherever possible. Bars indicate 95% CI on the proportion.

Eight studies provided prevalence estimates stratified by age and sex.[17,18,26,38,40,43,44,47] Prevalence estimates were heterogeneous even within age and sex subgroups (Figure 3). Prevalence of moderate stenosis was higher in men than in women <70 years, being, on average 4.8% (95% CI, 3.1% to 7.3%) in men and 2.2% (95% CI, 0.9% to 4.9%) in women. In those age >70, prevalence estimates were higher, being, on average, 12.5% (95% CI, 7.4% to 20.3%) in men and 6.9% (95% CI, 4.0% to 11.5%) in women. One included study[47] examined a birth cohort at age 78 and had an exceptionally high prevalence estimate (22.5%; range in other studies, 0% to 15.1%). Exclusion of this study altered the results in those age >70 to 10.7% (95% CI, 6.6% to 16.9%) in men and 5.8% (95% CI, 3.7% to 9.1%) in women.

Metaregression analysis showed that both age and sex had a significant influence on the prevalence of moderate stenosis. There was an estimated increase in prevalence of moderate stenosis for older age and male sex (Table 2). The estimated between-study variance was reduced from 0.20 to 0.10. There was no significant effect of study size, publication year, geographic region, assessment method, and study quality on moderate stenosis prevalence estimates (Table 2). Examination of the funnel plot (not shown) demonstrated that there was no asymmetry for studies on prevalence of moderate carotid artery stenosis (Egger's test $P=0.438$).

Severe Carotid Artery Stenosis

For the analysis of severe carotid artery stenosis (≥70%), only 4 studies, totaling 6518 individuals, provided data.[36,41,45,47] Overall, the prevalence of severe stenosis ranged from 0% to 4.9%, with a pooled random-effects prevalence estimate of 1.7% (95% CI, 0.7% to 3.9%). Stratified analysis and metaregression analysis were not attempted for prevalence of severe stenosis analysis given the paucity of studies.

Discussion

We conducted a systematic review of studies addressing the prevalence of moderate and severe carotid artery stenosis and a metaregression analysis to understand the reasons for estimate variability. Our findings show that the prevalence of moderate stenosis increases with age in both men and women, but that men at all ages have the highest prevalence estimates. Different age and sex distribution across studies explained half of the heterogeneity in prevalence estimates. The number of studies that allowed meaningful data synthesis of severe stenosis was limited.

Information on the prevalence of asymptomatic carotid stenosis may provide insight into the planning and allocation of funds for screening methods to detect patients who may benefit from carotid endarterectomy. Although there are sufficient data to provide reliable age- and sex-specific prevalence estimates of moderate stenosis, there are limited data on prevalence estimates of severe stenosis available in the literature. At present, there is considerable variation among studies with respect to cutoff point used for severe

Table 2. Effect of Covariates on Prevalence of Moderate Carotid Artery Stenosis (Random Effects Models)

	Estimate (SE)*	*P* Value
Univariable metaregression analyses		
Participant characteristics		
Age	0.067 (0.017)	<0.001
Female (%)	−0.012 (0.009)	0.219
Study characteristics		
Study size		
1000 or more	Reference	
500–999	−0.285 (0.449)	0.526
<500	0.033 (0.393)	0.399
Publication year		
2000 or later	Reference	
1990–1999	0.298 (0.339)	0.380
Before 1990	−0.592 (0.482)	0.220
Geographic region		
America	Reference	
Europe	−0.247 (0.364)	0.497
Asia	−0.396 (0.514)	0.441
Assessment method (duplex vs doppler)	−0.073 (0.644)	0.910
Study quality		
Representative of general population	−0.025 (0.353)	0.943
Appropriate recruitment	0.256 (0.333)	0.443
Adequate response rate	−0.022 (0.339)	0.949
High/low study quality†	0.180 (0.339)	0.595
Multivariable metaregression analyses		
Intercept	−7.348 (1.099)	
Age	0.080 (0.017)	<0.001
Female (%)	−0.022 (0.007)	0.003

*Parameter estimates (SEs) are presented on a logit scale. The estimated prevalence of moderate stenosis, given particular values of the covariates, can be derived from the regression equation. For example, the estimated logit (prevalence) for women at age 60 is given by $-7.348+0.080\times60-0.022\times100=-4.71$, which corresponds to a prevalence of moderate stenosis of $\exp(-4.71)=0.9\%$.

†High-quality studies had 2 of more of the 3 high-quality criteria. See Methods for details.

stenosis (70%, 75%, and 80% stenosis). Moreover, the method of measurement used, ie, NASCET or ECST, which was not always reported, may also have influenced the estimates. As a result, no reliable age- and sex-specific prevalence estimates for severe stenosis could be provided, while probably only asymptomatic patients with severe stenosis are at high enough risk to justify carotid endarterectomy.[10,11,14] To resolve this lack of accurate age- and sex-specific prevalence estimates of severe stenosis, we might ask original investigators for stratified analyses for the degree of stenosis of interest. However, in that case, we might as well ask for the individual patient data. The latter would allow recoding of variables, more flexible analyses, and more advanced modeling techniques.

We observed that moderate stenosis was more prevalent among men than women, and there was an increasing prevalence with age, which confirms previous findings.[26,29–31,39,45] Given that carotid endarterectomy also appeared to be more beneficial in men than women,[13,14] this might imply that screening for asymptomatic carotid stenosis might be more worthwhile among men with reasonable life expectancy than among women. However, treatment choice requires a comparison of acute treatment-related risks and future stroke risk, and only a well-designed decision analysis can gain the best possible insight in the balance of risks and benefits. Such analysis can also determine whether screening would be effective in the entire population or in subgroups according to age or sex only. Therefore, further research is required to identify those individuals with asymptomatic stenosis who might derive the most benefit from preventive treatment.

This study has several limitations. First, the stratified prevalence estimates may have been influenced by the relatively small number of studies that provided age- and sex-specific data. Another limitation concerns nonresponse within the included studies. As nonresponse increases with age and asymptomatic carotid stenosis is more prevalent in older patients, the overall prevalence estimates may have been underestimated. Third, the studies included in this review used different methods to determine the degree of stenosis, ie, duplex or Doppler alone. Duplex screening has been shown to be an accurate method for assessing carotid stenosis[56] and is the most frequently used method nowadays. Doppler screening alone has been shown to be less accurate than duplex screening and tends to underestimate the degree of stenosis. Metaregression showed that the overall prevalence estimates of moderate stenosis, however, did not essentially differ between studies that used the duplex assessment method and those that used Doppler alone. In addition, we reviewed whether the included studies reported the method of measurement of stenosis (ie, NASCET or ECST method), because it has been shown that the NASCET method results in lower estimates of the degree of stenosis compared with the ECST method.[57] Unfortunately, only a few studies provided details about the method of measurement used. Because of the lack of information about which method of measurement was used, we were unable to convert stenosis values to 1 uniform method. Surprisingly, metaregression showed that quality features did not significantly add to the variation in prevalence estimates of moderate stenosis. Our quality scoring method may, however, not have entirely captured all methodologic aspects. Alternatively, the seemingly considerable number of studies (N=29) may still have been too small to yield sufficient statistical power for conducting metaregression analyses. We think, however, that factors such as average age and sex may be much stronger determinants, ie, may have overruled methodologic quality of the studies.

In conclusion, we noted that good stratified prevalence estimations are difficult to extract from the literature. Collaborative efforts with pooled analysis of individual patient data are needed to estimate the prevalence of asymptomatic carotid stenosis in subgroups more accurately. Such data can then also be used to explore whether screening and treatment

of carotid artery stenosis in asymptomatic patients would be worthwhile.

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Disclosures

None.

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